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Persistence of long-term COVID-19 sequelae in patients with cancer: an analysis from the OnCovid registry.

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Running: COVID-19 sequelae in patients with cancer.

Persistence of long-term COVID-19 sequelae in patients with cancer: an analysis from the OnCovid registry.

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ABSTRACT

Introduction: A significant proportion of patients with cancer who recover from COVID-19 may experience COVID-19 sequelae in the early post-infection phase, which negatively affect the continuity of care and oncological outcome. The long-term prevalence and clinical impact of post-COVID-19 syndrome in patients with cancer are largely unknown.

Methods: In this study, we describe the time course of COVID-19 sequelae in patients with non-advanced cancers enrolled into the OnCovid registry.

Results: Overall, 186 patients were included, with a median observation period of 9.9 months (95%CI:8,8-11.3) post COVID-19 resolution. After a median interval of 2.3 months post-COVID-19 (interquartile range: 1.4-3.7), 31 patients (16.6%) reported ≥ 1 sequelae, including respiratory complications (14, 7.6%), fatigue (13, 7.1%), neuro-cognitive sequelae (7, 3.8%). The vast majority of the patients were not vaccinated prior to COVID-19. COVID-19-related sequelae persisted in 9.8% and 8% of patients 6 and 12 months after COVID-19 resolution. Persistence of sequelae at first oncological follow-up was associated with history of complicated COVID-19 (45.2% vs 24.8%, $p=0.0223$), irrespective of oncological features at COVID-19 diagnosis.

Conclusion: This study confirms for the first time that, in a largely unvaccinated population, post-COVID-19 syndrome can affect a significant proportion of patients with non-advanced cancer who recovered from the acute illness. COVID-19 sequelae may persist up to 12 months in some patients, highlighting the need for dedicated prevention and supportive strategies.

BRIEF COMMUNICATION

Introduction

A significant proportion of Coronavirus Disease 2019 (COVID-19) survivors are at risk of developing post-COVID-19 syndrome¹, a complex manifestation of likely immune-inflammatory pathogenesis that is characterized by a wide variety of symptoms including persistent fatigue, neuro-cognitive sequelae and varying degrees respiratory impairment. Evidence in non-cancer populations suggests chronic consequences from COVID-19 to persist beyond 6 months post-infection^{2,3}.

Patients with cancer are especially vulnerable to COVID-19^{4,6}, and recent evidence from the OnCovid study suggests that at least 15% of those who outlive the acute phase of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection can experience COVID-19 sequelae, which significantly affect the continuity of their oncological care and survival outcome, independent of oncological prognostic factors⁷.

There is no evidence to suggest whether post-COVID-19 syndrome can lead to long-term consequences in patients with cancer. In this study, we evaluated OnCovid registry participants with non-advanced cancer, to estimate prevalence, duration and clinical significance of long-term sequelae from COVID-19.

Patients and Methods

OnCovid (NCT04393974) is an active European registry study that, since the beginning of the pandemic, has collected consecutive patients fulfilling the following inclusion criteria: 1) age ≥ 18 years; 2) diagnosis of SARS-CoV-2 infection confirmed by RT-PCR of a nasopharyngeal swab; 3) history of solid or hematologic malignancy, at any time during the patients' past medical history, either active or in remission at the time of COVID-19 diagnosis.

By the data lock of 22nd of December 2021, the registry included 3237 consecutive patients from 36 institutions across 6 countries (UK, Italy, Spain, France, Belgium and Germany), and included patients diagnosed with COVID-19 between the 27th of February 2020 and the 30th of November 2021. A list of the participating centers with eligible patients for this analysis is provided in **Supplementary Table 1**.

We evaluated long-term outcomes in patients with non-advanced cancer who had survived COVID-19 by describing the prevalence and natural history of COVID-19 sequelae over time. For this purpose, we included only patients who underwent a clinical reassessment 6-months after COVID-19 diagnosis at each participating institution.

Acknowledging the competing influence of underlying malignancy in affecting symptomatic burden and survival post-COVID-19, patients with advanced/metastatic malignancy were excluded from the analysis to avoid bias in the attribution of causality of long-term sequelae.

The clinical definitions of symptoms, clinical syndromes, complications from COVID-19 followed standardized criteria published by the World Health Organization⁸. However, these were assessed by treating physicians as per local practice and when clinically indicated, for instance during clinical consultation, symptoms review, physical examination, imaging and/or laboratory findings review. Timing of follow-up was not standardized but dictated by the discretion of treating physicians as per standard of care.

COVID-19 sequelae were categorized according to the system/organ involved into: respiratory symptoms (including dyspnoea and chronic cough), residual fatigue, neuro-cognitive sequelae (including cognitive, visual impairment, and/or dysosmia - age/dysgeusia, headache, confusion, lethargy), and others (including other organs disfunctions, weight loss, residual fever, muscle cramps, arthralgia, skin conditions, etc). Additionally, sequelae were also differentiated as single-site and multiple-sites, in case of patients experiencing multiple sequelae.

First, we documented prevalence and type of COVID-19 sequelae at the time of first oncological assessment post-COVID-19 and their distribution according to key demographics, oncological and COVID-19-related characteristics, including the receipt of SARS-CoV-2 vaccines prior to the infection. We also evaluated patterns of resumption of systemic anticancer therapy (SACT) at the first reassessment among patients who were on SACT within 4 weeks of COVID-19 diagnosis. Lastly, we described prevalence and type of COVID-19 sequelae at 6 and 12-months following recovery from SARS-Cov-2 infection (+/- 28 days). Detailed methodology is provided in **Supplementary Methods**.

Results

The eligible study population consisted of 3108 patients. After the exclusion of patients with advanced/metastatic disease and those who had not undergone a 6-months reassessment and those who experienced SARS-CoV-2 re-infection during follow-up, 186 patients were included in this analysis (**Figure 1**).

The first reassessment was performed as per local practice, with a median interval of 2.3 months (inter quartile range: 1.4-3.7) from COVID-19 diagnosis. This coincided with the 6 months follow-up assessment for 40 patients. Overall, 31 patients (16.6%) experienced at least one COVID-19 complication, including respiratory sequelae (14,

7.6%), post COVID-19 fatigue (13, 7.1%), neuro-cognitive sequelae (7, 3.8%) and others (7, 3.8%) (**Figure 2A**); 7 patients (3.7%) experienced >1 sequelae. The median post COVID-19 follow-up was 9.9 months (95%CI: 8.8-11.3) and with only 12 events, the median post-COVID-19 survival was not reached.

Patients suffering from sequelae at the first post-COVID-19 reassessment were more likely smokers (68% vs 38.5%, $p=0.007$) and had history of complicated COVID-19 (45.2% vs 24.8%, $p=0.0223$) (**Figure 2B**). No associations between sequelae and oncological features, including the receipt of SACT within 4 weeks of COVID-19, were reported. The proportion of patients experiencing oncological disease progression at the first reassessment was comparable in patients with and without sequelae ($p=0.2335$). The vast majority of the patients were not vaccinated prior to COVID-19 (**Table 1**). Among the 75 patients (40.8%) who were on SACT at COVID-19, 15 (20%) permanently discontinued treatment, 8 (10.7%) resumed treatment following dose/regimen adjustments.

At the 6-months' follow up, COVID-19 sequelae were reported for 18 patients (9.8%), of whom 5 (2.7%) had multiple symptoms. In detail, 9 patients (4.9%) experienced respiratory sequelae, 6 patients (3.2%) experienced post COVID-19 fatigue, 4 patients (2.2%) neuro-cognitive sequelae and 5 patients (2.7%) had sequelae of other kinds (**Figure 2A**). Disease progression at 6-months was reported for 9 patients among those experiencing sequelae (50%) and for 54 (32.5%) among those who did not experienced sequelae ($p=0.1390$).

Data on oncological follow up at 12-months was available for 100 patients; among them 8 (8%) experienced COVID-19 sequelae and 2 patients (2%), multiple-sites sequelae. In detail, 3 patients (3%) reported respiratory sequelae, 3 (3%) post COVID-19 fatigue (**Figure 2A**). Disease progression at 12-months was reported for 5 patients and 39 patients in the sequelae and non-sequelae subgroups, respectively (62.5% vs 42.4%, $p=0.2951$).

Discussion

In the context of a progressive improvement in terms of disease management, hospital/testing capacity, and vaccinal campaigns⁹, post-COVID syndrome continues to pose a threat to the wellbeing of patients with cancer.

Although including only patients with non-advanced tumours, with a likely lower burden of cancer-related symptoms, this study confirms our previous findings in unselected patients with cancer¹⁰. At least ~15% of COVID-19 survivors can experience sequelae during the early post-infection phase, independent of major demographic and tumour characteristics. Features of COVID-19 severity, such as complications from COVID-

19 appear the strongest determinants. Whilst prevalence of COVID-19 sequelae decreases over time, a significant proportion of patients experiences persisting symptoms following up to 12 months from recovery. We confirm respiratory symptoms to be the most prevalent sequelae from COVID-19, although we reported a non-negligible proportion of neuro-cognitive sequelae, providing further credence to the role of neuroinflammation as a pathogenic underlying mechanism¹¹⁻¹³.

Our findings mirror those reported among the general population, where between 13% and 60% of COVID-19 survivors are at risk of developing post COVID-19 symptoms^{3,14-16}. In addition, estimates of symptoms' prevalence during the early post-infection phase for the general population reach >30%¹⁷, and up to 25% of patients may report sequelae beyond the 6-months landmark¹⁵.

Whilst limited by the selection of non-advanced cancer patients and by the non-standardised follow-up, due to patients being re-evaluated according to local practice, this study is the first to provide a comprehensive portrait of the long-term impact of post-COVID-19 syndrome in patients with cancer. Whilst COVID-19 sequelae seem to affect a minority of patients recovered from the acute infection, 8% of them remain symptomatic up to a year after recovery, highlighting the need of dedicated preventative and supportive strategies. Further evidence is required to evaluate the preventative role of SARS-Cov-2 vaccines in protecting cancer patients from long-term sequelae from COVID-19.

Role of the funding source

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Data availability statement

The data underlying this article cannot be shared publicly in accordance with current regulations on data protection. The data will be shared on reasonable request to the corresponding author.

Ethical approval and consent to participate

OnCovid was granted central approval by the United Kingdom Health Research Authority (20/HRA/1608) and by the corresponding research ethics committees at each participating institution. Full waiver of consent due to the retrospective nature of the study was granted by the UK HRA in accordance with UK law.

Authors' Contributions

All authors contributed to the publication according to the ICMJE guidelines for the authorship. All authors read and approved the submitted version of the manuscript (and any substantially modified version that involves the author's contribution to the study). Each author has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Consent for Publication

Informed consent was waived by competent authorities due to anonymized nature of patient data and retrospective design of the study.

Availability of Data and Material

Study data made available upon reasonable request.

Competing Interests

Alessio Cortellini received consulting fees from MSD, BMS, AstraZeneca, Roche; speakers' fee from AstraZeneca, MSD, Novartis and Eisai.

David J Pinato received lecture fees from ViiV Healthcare, Bayer Healthcare, BMS, Roche, Eisai, Falk Foundation, travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, Eisai, Roche, DaVolterra and Astra Zeneca; research funding (to institution) from MSD and BMS.

Alex Prat has declared personal honoraria from Pfizer, Roche, MSD Oncology, Eli Lilly, and Daiichi Sankyo; travel, accommodations, and expenses paid by Daiichi Sankyo; research funding from Roche and Novartis; and consulting/advisory role for NanoString Technologies, Amgen, Roche, Novartis, Pfizer and Bristol-Myers Squibb.

Matteo Lambertini acted as consultant for Roche, Novartis, Lilly, AstraZeneca, Exact Sciences, MSD, Pfizer, Seagen and received speaker honoraria from Roche, Novartis, Lilly, Pfizer, Takeda, Ipsen and Sandoz outside the submitted work.

Thomas Newsom-Davis has declared consulting/advisory role for Amgen, Bayer, AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Otsuka, Pfizer, Roche, and Takeda; speakers fees from AstraZeneca, MSD, Roche, Takeda and travel, accommodations and expenses paid by AstraZeneca, BMS, Boehringer Ingelheim, Lilly, MSD, Otsuka, Roche, and Takeda.

Joan Brunet has declared consulting/advisory role for MSD and Astra Zeneca.

Alessandra Gennari has declared consulting/advisory role for Roche, MSD, Eli Lilly, Pierre Fabre, Eisai, and Daiichi Sankyo; speakers bureau for Eisai, Novartis, Eli Lilly, Roche, Teva, Gentili, Pfizer, Astra Zeneca, Celgene, and Daiichi Sankyo; research funds: Eisai, Eli Lilly, and Roche. CMV has received travel grants and other honoraria from BMS, MSD, Novartis and Roche.

Gianluca Gaidano has declared consulting/advisory role for Janssen, Abbvie, AstraZeneca and BeiGene, and speaker fees from Janssen and Abbvie.

Lorenza Rimassa received consulting fees from Servier, Amgen, ArQule, AstraZeneca, Basilea, Bayer, BMS, Celgene, Eisai, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Lilly, MSD, Nerviano Medical Sciences, Roche, Sanofi, Zymeworks; lecture fees from AbbVie, Amgen, Bayer, Eisai, Gilead, Incyte, Ipsen, Lilly, Merck Serono, Roche, Sanofi; travel expenses from Ipsen; and institutional research funding from Agios, ARMO BioSciences, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Zymeworks. All remaining authors have declared no conflicts of interest.

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Table 1: Distribution of baseline demographics, tumour and COVID-19 characteristics at the first re-assessment according to COVID-19 sequelae experiencing. *Within 4 weeks of COVID-19 diagnosis.

	Without COVID-19 Sequelae N = 153 (%)	With COVID-19 Sequelae N = 31 (%)	P value
Contry			
United Kingdom	54 (35.3)	8 (25.8)	0.5927
Spain	55 (35.9)	13 (41.9)	
Italy	44 (28.8)	10 (32.3)	
Sex			
Male	77 (50.3)	15 (48.4)	0.8443
Females	76 (49.7)	16 (51.6)	
Age			
<65 years	67 (43.8)	14 (45.2)	0.8888
≥65 years	86 (56.2)	7 (54.8)	
Comorbidities			
0-1	85 (55.6)	14 (45.2)	0.2911
≥2	68 (44.4)	17 (54.8)	
Smoking history			
Never smokers	75 (61.5)	8 (32)	0.0070
Former/current smokers	47 (38.5)	17 (68)	
Missing	31	6	
Primary Tumour			
Breast	44 (28.8)	6 (20)	0.8850
Gastrointestinal	29 (19)	6 (20)	
Gynaecological/Genito-Urinary	32 (20.9)	7 (23.3)	
Thoracic	13 (8.5)	4 (13.3)	
Others	19 (12.4)	3 (10.0)	
Haematological	16 (10.5)	4 (13.3)	
Missing	0	1	
SACT at COVID-19 diagnosis*			
No	94 (62.7)	19 (63.3)	0.9452
Yes	56 (37.3)	11 (36.7)	
Missing	3	1	
COVID-19 therapy			
No	59 (40.4)	9 (31)	0.3454
Yes	87 (59.6)	20 (69)	
Missing	7	2	
Complicated COVID-19			
No	115 (75.2)	17 (54.8)	0.0223
Yes	38 (24.8)	14 (45.2)	
Hospitalization			
Not required	48 (31.8)	8 (25.8)	0.7847
Required	83 (55.0)	19 (61.3)	
Pre-existing	20 (13.2)	4 (12.9)	
Missing	2	-	
Vaccination status prior to COVID-19			
Unvaccinated	138 (93.9)	31 (100)	0.3681
Fully vaccinated	3 (2)	-	
Partially vaccinated	6 (4.1)	-	
Missing	6	-	
Disease progression at 1st assessment			
No	119 (77.8)	21 (67.7)	0.2335
Yes	34 (22.2)	10 (32.3)	

Figure Legends.

Figure 1: study flow diagram.

Figure 2: prevalence of COVID-19 sequelae. **A)** Prevalence at the first clinical reassessment (31/184: 16%), at 6-months (18/184: 9.8%), and at 12-months (8/100: 8%). Type of sequelae at the first reassessment: respiratory sequelae (14: 7.6%), fatigue (13: 7.1%), neuro-cognitive sequelae (7: 3.8%), others (7: 3.8%). Type of sequelae at the 6-months reassessment: respiratory sequelae (9: 4.9%), fatigue (6: 3.2%), neuro-cognitive sequelae (4: 2.2%), others (5: 2.7%). Type of sequelae at the 12-months reassessment: respiratory sequelae (3: 3%), fatigue (3: 3%), neuro-cognitive sequelae (1: 1%), others (3: 3%). **B)** Prevalence of COVID-19 sequelae at the first reassessment among never smokers (8/83: 9.6%), current/former smokers (17/64: 26.6%), and among patients who did not experience prior complications from COVID-19 (17/132: 12.9%), and those who experienced complicated COVID-19 (14/52: 26.9%).

Highlights

- Patients with cancer may experience “long-COVID”
- We evaluated long-term sequelae from COVID-19 across OnCovid registry participants
- A significant proportion of patients may experience long-term COVID-19 sequelae.

CONFLICT OF INTEREST STATEMENT

Persistence of COVID-19 sequelae in patients with cancer: analysis of long-term outcomes from the OnCovid registry.

As corresponding author of the abovementioned manuscript, I declare on behalf of my co-authors the following conflict of interests:

Alessio Cortellini received consulting fees from MSD, BMS, AstraZeneca, Roche; speakers' fee from AstraZeneca, MSD, Novartis and Eisai.

David J Pinato received lecture fees from ViiV Healthcare, Bayer Healthcare, BMS, Roche, Eisai, Falk Foundation, travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, Eisai, Roche, DaVolterra and AstraZeneca; research funding (to institution) from MSD and BMS.

Alex Prat has declared personal honoraria from Pfizer, Roche, MSD Oncology, Eli Lilly, and Daiichi Sankyo; travel, accommodations, and expenses paid by Daiichi Sankyo; research funding from Roche and Novartis; and consulting/advisory role for NanoString Technologies, Amgen, Roche, Novartis, Pfizer and Bristol-Myers Squibb.

Matteo Lambertini acted as consultant for Roche, Novartis, Lilly, AstraZeneca, Exact Sciences, MSD, Pfizer, Seagen and received speaker honoraria from Roche, Novartis, Lilly, Pfizer, Takeda, Ipsen and Sandoz outside the submitted work.

Thomas Newsom-Davis has declared consulting/advisory role for Amgen, Bayer, AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Otsuka, Pfizer, Roche, and Takeda; speakers fees from AstraZeneca, MSD, Roche, Takeda and travel, accommodations and expenses paid by AstraZeneca, BMS, Boehringer Ingelheim, Lilly, MSD, Otsuka, Roche, and Takeda.

Joan Brunet has declared consulting/advisory role for MSD and AstraZeneca.

Alessandra Gennari has declared consulting/advisory role for Roche, MSD, Eli Lilly, Pierre Fabre, Eisai, and Daiichi Sankyo; speakers bureau for Eisai, Novartis, Eli Lilly, Roche, Teva, Gentili, Pfizer, AstraZeneca, Celgene, and Daiichi Sankyo; research funds: Eisai, Eli Lilly, and Roche. CMV has received travel grants and other honoraria from BMS, MSD, Novartis and Roche.

Gianluca Gaidano has declared consulting/advisory role for Janssen, Abbvie, Astra-Zeneca and BeiGene, and speaker fees from Janssen and Abbvie.

Lorenza Rimassa received consulting fees from Servier, Amgen, ArQule, AstraZeneca, Basilea, Bayer, BMS, Celgene, Eisai, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Lilly, MSD, Nerviano Medical Sciences, Roche, Sanofi, Zymeworks; lecture fees from AbbVie, Amgen, Bayer, Eisai, Gilead, Incyte, Ipsen, Lilly, Merck Serono, Roche, Sanofi; travel expenses from Ipsen; and institutional research funding from Agios, ARMO BioSciences, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Zymeworks.

All remaining authors have declared no conflicts of interest.

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Alessio Cortellini